SUPPORTING INFORMATION

The dopamine, serotonin and norepinephrine releasing activities of a series of methcathinone analogs in male rat brain synaptosomes

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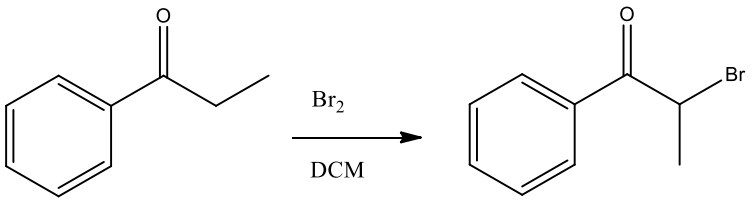
Synthetic Chemistry

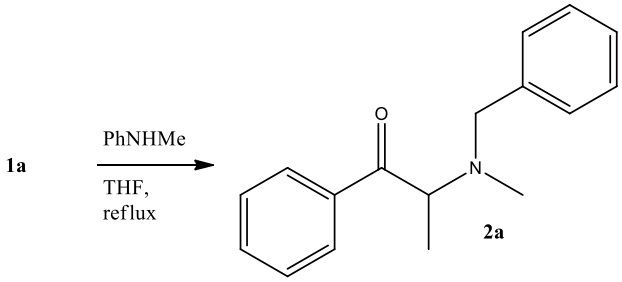
General Preparation of Methcathinone Analogs (Described for methycathinone).

Preparation of 2-Bromo-1-Phenyl-1-oxopropane (1a).



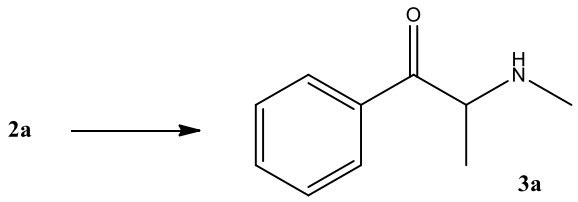
Propiophenone (2 g, 14.9 mmol) was dissolved in dichloromethane (70 mL) and treated with bromine (2.62 g, 16.4 mmol) and stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the organic phase was separated, washed with brine, dried ($MgSO_4$) and concentrated to yield 3.08 g (97%) of **1a** as a pale yellow oil, which required no further purification. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 8.03 (d, 2 H, J = 6 Hz), 7.65-7.58 (m, 1 H), 7.50 (dd, 2 H, J = 3 Hz, 6 Hz), 5.38-5.30 (m, 1 H), 1.93 (d, 3 H, J = 6 Hz).

Preparation of 2-(N-Benzyl-N-Methylamino)-1-Phenyl-1-oxopropane (2a).



A solution of **1a** (3.08 g, 14.4 mmol) and N-benzylmethylamine (4.38 g, 36.1 mmol) in THF (60 mL) was refluxed for 18 h. The reaction mixture was concentrated and the residue was taken up into ethyl acetate and washed with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by automated flash chromatography (silica gel, 4/1 hexane/ethyl acetate) to yield 2.93 g (80%) of yellow oil (**2a**). ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.99 (dd, 1 H, J = 3 Hz, 6 Hz), 7.60-7.52 (m, 1 H), 7.46-7.43 (m, 2 H), 7.28-7.21 (m, 5 H), 4.34-4.28 (m, 1 H), 3.63 (s, 2 H), 2.22 (s, 3 H), 1.31 (d, 3 H, J = 6 Hz).

Preparation of 2-(Methylamino)-1-Phenyl-1-oxopropane hydrochloride (1)



A solution of **2a** (2.5 g, 9.9 mmol) and 1-chloroethyl chloroformate (2.15 mL, 19.7 mmol) in dichloroethane (100 mL) was refluxed for 2 h. The reaction mixture was concentrated and the residue was dissolved in methanol (100 mL) and refluxed for 1 h. The solids were filtered, washed with ether and dried to obtain 2.3 g of grey solid. The crude material was recrystallized from ethyl acetate/methanol to yield 1.4 g (72%) of grey solid (**1**). Mp = 183-185 C (dec.);-^{1}H NMR (CD_3OD 300 MHz) δ 8.10-8.02 (m, 2 H), 7.78-7.72 (m, 1 H), 7.66-7.58 (m, 2 H), 5.17-5.07 (m, 1 H), 2.78 (s, 3 H), 1.57 (d, 3 H, J = 6 Hz); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 196.3, 134.6, 132.8, 129.1, 128.7, 58.1, 30.6, 15.3; ESI-MS, calculated for $C_{10}H_{13}NO$ $(M+H)^+$ 164.2; observed 164.3; Anal. Calculated for $C_{10}H_{14}ClNO$; C, 60.15; H, 7.07; N, 7.01. Found: C, 60.28; H, 7.13; N, 7.02.

The general procedure described above was used to synthesize the following analogs:

2-(Methylamino)-1-(3-Bromophenyl)-1-oxopropane hydrochloride (11): The product was isolated as a white solid in 54% yield (1.19 g), mp = 193-195 C (dec.); ^{1}H NMR (D_2O, 500 MHz) δ 8.10 (s, 1 H), 7.88 (dd, 1 H, J= 9 Hz), 7.44 (dd, 1 H, J = 9 Hz), 5.01-4.93 (m, 1 H), 2.71 (s, 3 H), 1.50 (d, 3 H, J = 6 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 138.8, 132.7, 132.2, 128.8, 60.7, 31.7, 15.9; ESI-MS, calculated for $C_{10}H_{12}BrNO$ $(M+H)^+$ 243.1; observed 241.9; Anal. Calculated for $C_{10}H_{13}BrClNO$; C, 43.11; H, 4.70; N, 5.03. Found: C, 43.13; H, 4.77; N, 5.05.

2-(Methylamino)-1-(3-Fluorophenyl)-1-oxopropane hydrochloride (13): The product was isolated as a white solid in 93% yield (4.68 g), mp = 164-166 C; ^{1}H NMR (D_2O, 500 MHz) δ 7.83 (d, 1 H, J = 2.0 Hz), 7.75 (d, 1 H, J= 4.5 Hz), 7.67-7.62 (m, 1 H), 7.55-7.50 (m,1 H), 5.11-5.05 (m, 1 H), 2.82 (s, 3 H), 1.61 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 164.3, 134.3, 131.4, 125.0, 122.4, 115.5, 59.8, 31.0, 15.1; ESI-MS, calculated for $C_{10}H_{12}FNO$ $(M+H)^+$ 182.2; observed 182.0; Anal. Calculated for $C_{10}H_{13}ClFNO$; C, 55.18; H, 6.02; N, 6.43. Found: C, 55.17; H, 6.05; N, 6.44.

2-(Methylamino)-1-[(3-Trifluoromethyl)phenyl]-1-oxopropane hydrochloride (14): The product was isolated as a grey solid in 88% yield (1.9 g), mp = 160-162 C; ^{1}H NMR (D_2O, 300 MHz) δ 8.24 (s, 1 H), 8.18-8.12 (m, 1 H), 8.01-7.96 (m, 1 H), 7.75-7.68 (m, 1 H), 5.10-5.02 (m, 1 H), 2.73 (s, 3 H), 1.51 (d, 3 H, J = 6 Hz); ESI-MS, calculated for

$C_{11}H_{12}F_3NO$ $(M+H)^+$ 232.2; observed 232.3; Anal. Calculated for $C_{11}H_{13}ClF_3NO$; C, 49.36; H, 4.90; N, 5.23. Found: C, 49.64; H, 4.90; N, 5.18.
2-(Methylamino)-1-[(3-Trifluoromethyl)phenyl]-1-oxopropane: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.4, 130.2, 125.7, 59.0, 32.1, 31.0, 15.0.

2-(Methylamino)-1-(3-Trifluoromethoxyphenyl)-1-oxopropane hydrochloride (15): The product was isolated as a white solid in 52% yield (1.6 g), mp = 160-161 C; ^1H NMR (D_2O, 300 MHz) δ 7.90-7.86 (m, 1 H), 7.81 (s, 1 H), 7.61-7.55 (m, 2 H), 4.86-4.77 (m, 1 H), 2.54 (s, 3 H), 1.40 (d, 3 H, J = 6 Hz); ESI-MS, calculated for $C_{11}H_{12}F_3NO_2$ $(M+H)^+$ 248.2; observed 248.2; Anal. Calculated for $C_{11}H_{13}ClF_3NO_2$; C, 46.58; H, 4.62; N, 4.94. Found: C, 46.45; H, 4.61; N, 5.00.
2-(Methylamino)-1-(3-Trifluoromethoxyphenyl)-1-oxopropane: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.3, 133.5, 129.5, 128.7, 126.7, 124.7, 59.9, 30.6, 14.6.

2-(Methylamino)-1-(3-Tolyl)-1-oxopropane hydrochloride (16): The product was isolated as a white solid in 94% yield (6.5 g), mp = 190-192 C (dec.); ^1H NMR (D_2O, 300 MHz) δ 7.77-7.69 (m, 2 H), 7.55-7.48 (m, 1 H), 7.45-7.36 (m, 1 H), 5.00-4.93 (m, 1 H), 2.68 (s, 3 H), 2.31 (s, 3 H), 1.48 (d, 3 H, J = 6 Hz); ESI-MS, calculated for $C_{11}H_{15}NO$ $(M+H)^+$ 178.2; observed 178.6; Anal. Calculated for $C_{11}H_{16}ClNO$; C, 61.82; H, 7.55; N, 6.55. Found: C, 61.70; H, 7.70; N, 6.57.
2-(Methylamino)-1-(3-Tolyl)-1-oxopropane: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.1, 130.9, 130.2, 129.0, 127.5, 126.6, 32.9, 32.3, 21.3, 10.8, 8.8.

2-(Methylamino)-1-(3-Methoxyphenyl)-1-oxopropane hydrochloride (17): The product was isolated as a white solid in 44% yield (915 mg), mp = 160-162 C (dec.); ^1H NMR (D_2O, 300 MHz) δ 7.53-7.42 (m, 3 H), 7.29-7.23 (m, 1 H), 4.97 (dd, 1 H, J = 6 Hz, 9 Hz), 3.76 (s, 3 H), 2.72 (s, 3 H), 1.49 (d, 3 H, J = 9 Hz); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 196.2, 159.6, 134.3, 130.3, 121.2, 120.7, 113.1, 58.2, 55.5, 30.6, 15.4; ESI-MS, calculated for $C_{11}H_{15}NO_2$ $(M+H)^+$ 194.2; observed 194.3; Anal. Calculated (with 0.3 mol water), for $C_{11}H_{16}ClNO_2$; C, 56.20; H, 7.12; N, 5.96. Found: C, 56.16; H, 7.00; N, 5.86.

2-(Methylamino)-1-(3-Nitrophenyl)-1-oxopropane hydrochloride (18): The product was isolated as a white solid in 76% yield (4.2 g), mp = 196-197 C (dec.); ^1H NMR (D_2O, 300 MHz) δ 8.72 (s, 1 H), 8.51-8.45 (m, 1 H), 8.30-8.24 (m, 1 H), 7.79-7.72 (m, 1 H), 5.04-4.96 (m, 1 H), 2.65 (s, 3 H), 1.47 (d, 3 H, J = 6 Hz); ESI-MS, calculated for $C_{10}H_{12}N_2O_3$ $(M+H)^+$ 209.2; observed 209.0; Anal. Calculated for $C_{10}H_{13}ClN_2O_3$; C, 49.09; H, 5.36; N, 11.45. Found: C, 49.10; H, 5.54; N, 11.24.
2-(Methylamino)-1-(3-Nitrophenyl)-1-oxopropane: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.6, 132.0, 130.0, 124.5, 60.9, 31.7, 15.7.

2-(Methylamino)-1-(4-Bromophenyl)-1-oxopropane hydrochloride (19): The product was isolated as a white solid in 40% yield (826 mg), mp = 217-218 C (dec.); ^1H NMR (CD_3OD, 300 MHz) δ 7.99 (d, 2 H, J = 9 Hz), 7.82 (d, 2 H, J = 9 Hz), 5.14-5.07 (m, 1 H), 2.79 (s, 3 H), 1.59 (d, 3 H, J = 6 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.9, 133.7, 131.6, 60.6, 31.7, 16.0; ESI-MS, calculated for $C_{10}H_{12}BrNO$ $(M+H)^+$ 243.1; observed 242.1; Anal.

Calculated for $C_{10}H_{13}BrClNO$; C, 43.11; H, 4.70; N, 5.03. Found: C, 43.00; H, 4.61; N, 4.93.

2-(Methylamino)-1-(4-Chlorophenyl)-1-oxopropane hydrochloride (20): The product was isolated as a white solid in 68% yield (1.11 g), mp = 212-213 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.05 (d, 2 H, J = 6 Hz), 7.63 (d, 2 H, J = 6 Hz), 5.14-5.06 (m, 1 H), 2.77 (s, 3 H), 1.57 (d, 3 H, J = 6 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 196.1, 131.7, 130.7, 60.7, 31.7, 16.1; ESI-MS, calculated for $C_{10}H_{12}ClNO$ $(M+H)^+$ 197.7; observed 197.7; Anal. Calculated for $C_{10}H_{13}Cl_2NO$; C, 51.30; H, 5.60; N, 5.98. Found: C, 51.55; H, 5.63; N, 5.91.

2-(Methylamino)-1-(4-Fluorophenyl)-1-oxopropane hydrochloride (21): The product was isolated as a white solid in 89% yield (5.49 g), mp = 224-225 C; ^{1}H NMR (D_2O, 300 MHz) δ 7.79-7.73 (m, 2 H), 7.02-6.96 (m, 2 H), 4.78-4.71 (m, 1 H), 2.44 (s, 3 H), 1.25 (d, 3 H, J = 6 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 196.1, 132.1, 132.0, 116.6, 116.3, 59.6, 31.0, 15.3; ESI-MS, calculated for $C_{10}H_{12}FNO$ $(M+H)^+$ 182.2; observed 182.1; Anal. Calculated for $C_{10}H_{13}ClFNO$; C, 55.18; H, 6.02; N, 6.43. Found: C, 55.27; H, 6.01; N, 6.37.

2-(Methylamino)-1-(4-Trifluoromethylphenyl)-1-oxopropane hydrochloride (22): The product was isolated as a white solid in 65% yield (2.0 g), mp = 214-216 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.08 (dd, 2 H, J = 6 Hz, 9 Hz), 7.82 (dd, 2 H, J = 6 Hz, 9 Hz), 5.03 (dd, 1 H, J = 6 Hz, 9 Hz), 2.71 (s, 3 H), 1.50 (d, 3 H, J = 9 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 196.5, 130.7, 129.5, 127.4, 127.3, 60.9, 31.7, 15.8; ESI-MS, calculated for $C_{11}H_{12}F_3NO$ $(M+H)^+$ 232.2; observed 232.3; Anal. Calculated for $C_{11}H_{13}ClF_3NO$; C, 49.36; H, 4.89; N, 5.23. Found: C, 49.37; H, 4.89; N, 5.35.

2-(Methylamino)-1-(4-Trifluoromethoxyphenyl)-1-oxopropane hydrochloride (23): The product was isolated as a white solid in 94% yield (2.07 g), mp = 212-214 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.01 (d, 2 H, J = 6 Hz), 7.40 (d, 2 H, J = 6 Hz), 4.96 (dd, 1 H, J = 6 Hz, 9 Hz), 2.72 (s, 3 H), 1.50 (d, 3 H, J = 9 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 195.9, 154.9, 132.8, 132.5, 123.4, 122.1, 60.7, 31.8, 16.0; ESI-MS, calculated for $C_{11}H_{12}F_3NO_2$ $(M+H)^+$ 248.2; observed 248.2; Anal. Calculated (with 0.2 mol water) for $C_{11}H_{13}ClF_3NO_2$; C, 45.99; H, 4.70; N, 4.87. Found: C, 45.85; H, 4.59; N, 5.01.

2-(Methylamino)-1-(4-Tolyl)-1-oxopropane hydrochloride (24): The product was isolated as a white solid in 71% yield (805 mg), mp = 223-225 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.95 (d, 2 H, J = 9 Hz), 7.42 (d, 2 H, J = 9 Hz), 5.09-5.01 (m, 1 H), 2.76 (s, 3 H), 2.45 (s, 3 H), 1.56 (d, 3 H, J = 6 Hz); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 129.6, 128.8, 58.1, 31.9, 30.6, 21.2, 15.4; ESI-MS, calculated for $C_{11}H_{15}NO$ $(M+H)^+$ 178.2; observed 178.4; Anal. Calculated for $C_{11}H_{16}ClNO$; C, 61.82; H, 7.55; N, 6.55. Found: C, 61.73; H, 7.55; N, 6.54.

2-(Methylamino)-1-(4-Methoxyphenyl)-1-oxopropane hydrochloride (25): The product was isolated as a white solid in 97% yield (5.8 g), mp = 208-209 C; ^{1}H NMR (D_2O, 300 MHz) δ 7.93 (d, 2 H, J = 9 Hz), 7.04 (d, 2 H, J = 9 Hz), 4.99-4.92 (m, 1 H),

3.83 (s, 3 H), 2.68 (s, 3 H), 1.50 (d, 3 H, J = 6 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 164.9, 131.7, 114.6, 59.3, 55.8, 31.0, 15.6; ESI-MS, calculated for $C_{11}H_{15}NO_2$ $(M+H)^+$ 194.2; observed 194.2; Anal. Calculated (0.1 mol water) for $C_{11}H_{16}ClNO_2$; C, 57.07; H, 7.05; N, 6.05. Found: C, 56.97; H, 6.93; N, 5.97.

2-(Methylamino)-1-(1-Naphthyl)-1-oxopropane hydrochloride (26): The product was isolated as a white solid in 19% yield (218 mg), mp = 195-197 C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.67-8.62 (m, 1 H), 8.26-8.21 (m, 1 H), 8.18-8.13 (m, 1 H), 8.05-7.99 (m, 1 H), 7.72-7.62 (m, 3 H), 5.26-5.18 (m, 1 H), 2.85 (s, 3 H), 1.52 (d, 3 H, J = 6 Hz); ESI-MS, calculated for $C_{14}H_{15}NO$ $(M+H)^+$ 214.2; observed 214.0; Anal. Calculated for $C_{14}H_{16}ClNO$; C, 67.33; H, 6.46; N, 5.61. Found: C, 67.15; H, 6.53; N, 5.62.
2-(Methylamino)-1-(1-Naphthyl)-1-oxopropane: ^{13}C NMR (d_6-DMSO 75 MHz) δ 131.2, 127.7, 127.6, 121.2, 59.8, 31.0, 15.0.

2-(Methylamino)-1-(2-Naphthyl)-1-oxopropane hydrochloride (27): The product was isolated as a grey solid in 94% yield (4.6 g), mp = 170-172 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.69 (s, 1 H), 8.09-7.97 (m, 4 H), 7.77-7.62 (m, 2 H), 5.33-5.22 (m, 1 H), 2.82 (s, 3 H), 1.66 (d, 3 H, J = 9 Hz); ESI-MS, calculated for $C_{14}H_{15}NO$ $(M+H)^+$ 214.3; observed 214.2; Anal. Calculated (with 0.6 mol water) for $C_{14}H_{16}ClNO$; C, 64.54; H, 6.65; N, 5.38. Found: C, 64.52; H, 6.73; N, 5.35.
2-(Methylamino)-1-(2-Naphthyl)-1-oxopropane: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.7, 132.8, 129.7, 129.1, 128.6, 127.6, 126.9, 124.0, 59.6, 34.7, 19.8.

2-(Methylamino)-1-(3-Indolyl)-1-oxopropane fumarate (28): The product was isolated as a white solid in 64% yield (54 mg), mp = 151-153 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.31 (s, 1 H), 8.25 (d, 1 H, J = 6 Hz), 7.50 (d, 1 H, J = 6 Hz), 7.32-7.23 (m, 1 H), 6.68 (s, 2 H), 4.78 (dd, 1 H, J = 6 Hz, 9 Hz), 2.73 (s, 3 H), 1.64 (d, 3 H, J = 9 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 131.3, 123.9, 122.9, 122.5, 111.4, 61.1, 34.6, 20.4; ESI-MS, calculated for $C_{12}H_{14}N_2O$ $(M+H)^+$ 203.2; observed 203.4; Anal. Calculated (with 0.1 mol water) for $C_{16}H_{182}O_5$; C, 60.03; H, 5.73; N, 8.75. Found: C, 59.96; H, 5.76; N, 8.91.

2-(Methylamino)-1-(3, 4-Dichlorophenyl)-1-oxopropane hydrochloride (29): The product was isolated as a white solid in 83% yield (5.1 g), mp = 205-207 C (dec.); ^{1}H NMR (D_2O, 300 MHz) δ 8.08 (s, 1 H), 7.78 (d, 1 H, J = 3 Hz), 7.65 (d, 1 H, J = 6 Hz), 4.98-4.91 (m, 1 H), 2.69 (s, 3 H), 1.49 (d, 3 H, J = 6 Hz);ESI-MS, calculated for $C_{10}H_{11}Cl_2NO$ $(M+H)^+$ 232.1; observed 232.4; Anal. Calculated for $C_{10}H_{12}Cl_3NO$; C, 44.72; H, 4.50; N, 5.22. Found: C, 44.90; H, 4.52; N, 5.22.
2-(Methylamino)-1-(3, 4-Dichlorophenyl)-1-oxopropane: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.2, 131.4, 130.9, 130.2, 129.7, 128.4, 125.2, 34.5, 32.8, 11.0, 9.0.

2-(Methylamino)-1-(3,4-Difluorophenyl)-1-oxopropane hydrochloride (30): The product was isolated as a white solid in 61% yield (1.29 g), mp = 213-215 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.10-7.92 (m, 2 H), 7.65-7.60 (m, 1 H), 5.16-5.04 (m, 1 H), 2.79 (s, 3 H), 1.59 (d, 3 H, J = 6 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 119.7, 119.4, 60.7,

31.7, 16.0; ESI-MS, calculated for $C_{10}H_{11}F_2NO$ $(M+H)^+$ 200.2; observed 200.1; Anal. Calculated for $C_{10}H_{12}ClF_2NO$; C, 50.97; H, 5.13; N, 5.94. Found: C, 51.22; H, 5.13; N, 5.95.

2-(Methylamino)-1-(3-Chloro-4-methylphenyl)-1-oxopropane hydrochloride (31):
The product was isolated as a grey solid in 89% yield (909 mg), mp = 207-208 C (dec.); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.04 (s, 1 H), 7.90 (d, 1 H, J = 9 Hz), 7.55 (d, 1 H, J = 9 Hz), 5.09 (dd, 1 H, J = 6 Hz, 9 Hz), 2.79 (s, 3 H), 2.48 (s, 3 H), 1.57 (d, 3 H, J = 9 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 195.8, 145.2, 136.5, 133.7, 133.0, 130.3, 128.5, 60.6, 31.7, 20.5, 16.1; ESI-MS, calculated for $C_{11}H_{14}ClNO$ $(M+H)^+$ 212.7; observed 212.1; Anal. Calculated for $C_{11}H_{15}Cl_2NO$; C, 53.24; H, 6.09; N, 5.64. Found: C, 53.19; H, 6.09; N, 5.66.